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(54) Title: IBUPROFEN TRITURATES AND TOPICAL COMPOSITIONS CONTAINING SAME

(57) Abstract

Ibuprofen forms a co-solution mixture which can be admixed with a vehicle to form a stable topical composition. Part of the menthol can be replaced by benzyl alcohol and the mixture can comprise also a pharmacologically acceptable alcohol, especially propylene glycol.

* See back of page

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(Case 1)

IBUPROFEN TRITURATES AND TOPICAL COMPOSITIONS CONTAINING SAME

The present invention relates to topical ibuprofen formulations.

Ibuprofen (ie. (isobutyl phenyl)propionic acid) is a white crystalline drug, insoluble in water but relatively soluble in organic solvents such as alcohol (1 in 1.5); chloroform (1 in 1); ether (1 in 2) and acetone (1 in 1.5).

Ibuprofen usually is taken orally and, although a number of topical formulations have been proposed, we are not aware of any satisfactory topical formulations. However, it often would be preferred to administer ibuprofen by topical application to an affected area so as to permit absorption through the skin. For example, in the treatment of rheumatic pain and/or inflammation, it is desirable to sustain a high local concentration of ibuprofen in the affected area of the body. Whereas oral administration to provide such local concentration would result in unacceptably high concentrations of ibuprofen throughout the body, topical application allows ibuprofen to accumulate only where it is needed.

In this connection, it is believed that solution dosage forms offer the best prospects of efficient percutaneous absorption of ibuprofen from topical formulations.

The present Applicants have experimented with topical formulations using conventional vehicles containing long chain cetyl and stearyl alcohols. They found that ibuprofen appears to react with these alcohols, thus reducing the concentration of the active ingredient for absorption. There was also a marked tendency for the ibuprofen to crystallise on storage as described above.

Mineral and vegetable oils dissolve ibuprofen but,

even at very high oil concentrations, the ibuprofen soon crystallises out. Oleic acid also dissolves ibuprofen but the solution has an unpleasant smell and is sticky and liable to autoxidation.

Vehicles based on combinations of oleic acid and medium chain length oils were investigated with various emulsifying agents - but avoiding cetyl and stearyl alcohols. These combinations prevented ibuprofen from crystallising out of an organic solution, but the emulsion formed could not be stiffened or settled sufficiently to withstand storage at 35 to 37°C for several months. Further, the H.L.B. (ie. hydrophilic-lipophilic balance) was higher than considered desirable for topical use.

Menthol (ie. 2-isopropyl-5-methylcyclohexanol) is a crystalline, naturally-occurring substance which has been used in pharmacy for at least a century. It has a penetrating odour and, for that reason, is widely used to relieve symptoms of bronchitis, sinusitis and similar conditions. It is used as an adjuvant in a number of topical formulations and has been reported to enhance the percutaneous transfer of systemically active, water-soluble or solubilizable drugs (see EP-A-0147146).

It has long been known that trituration of menthol with certain other crystalline substances, such as camphor (ie. 1,7,7-trimethylbicyclo(2,2,1)heptan-2-one), chloral hydrate (ie. 2,2,2-trichloroethane-1,1-diol) and phenol, forms a co-solution liquid or soft mass. However, we are not aware of any disclosure of trituration or admixture of menthol with a propionic acid derivative or of any other disclosure which would have led those skilled in the art of topical formulations to consider the use of menthol to overcome the problem of topically formulating ibuprofen.

JP-A-63179820 discloses that the bioavailability of water-soluble pharmacological agents in suppository preparations can be increased by adding the agent to the suppository base as a solution in a mixture of menthol and

camphor. Ibuprofen is included in the list of specified agents.

It has now surprisingly been found that ibuprofen and menthol (both crystalline substances) form a co-solution when mixed together. Whilst not wishing to be bound to any particular theory, it is believed that the two substances form a co-solution or eutectic solution when so mixed. Depending upon the relative proportions of the two components, one or both may be present partially in microcrystalline form.

The use of such a co-solution in a topical pharmaceutical composition leads to improved stability. Further, co-solution mixtures of ibuprofen and menthol can be formed in situ by mixing ibuprofen and menthol together with other components of a topical composition.

It also has been found that the amount of menthol required to provide a co-solution with ibuprofen can be reduced by the presence of benzyl alcohol as a co-solvent for the ibuprofen.

The present invention provides a composition comprising a co-solution mixture of ibuprofen and menthol. The invention further provides a topical pharmaceutical composition containing said mixture in a pharmacologically acceptable vehicle and the use of menthol to stabilize a topical composition comprising ibuprofen.

A liquid triturate can be formed by triturating the ibuprofen, menthol and optionally other components at ambient temperature and the triturate added to a vehicle to form the topical pharmaceutical composition of the invention. However, the triturate could be formed by heating the components together whilst triturating or by stirring or otherwise mixing a fused mass of the components and then cooling the hot mixture. Alternatively, the components can be compounded by dissolution in a suitable solvent, such as ethanol and the resultant solution (containing the co-solution mixture)

added to the vehicle.

Any relative proportions of ibuprofen and menthol which provide a co-solution mixture which is liquid at ambient temperature can be used. Suitably, the amount of ibuprofen by weight will be 10 to 70 percent based upon the weight of said mixture. However, said amount of ibuprofen preferably is 50 to 70 percent by weight.

Part of the menthol can be replaced by benzyl alcohol. When benzyl alcohol is present, it usually will replace 10 to 80, preferably 25 to 60, weight percent of the menthol.

It is preferred to include a pharmaceutically acceptable alcohol, especially a glycol such as propylene glycol or a Macrogol (ie. polyethylene glycol) in the liquid triturate of the invention when it is to be used to formulate a topical gel. When a triturate contains a glycol, it usually will be present in an amount by weight of up to 30 percent of the triturate. Preferably, said amount is 10 to 30 percent by weight and especially 20 to 25 percent by weight. However, substantially more glycol, eg. up to 70 percent by weight of the combined weight of ibuprofen, menthol, glycol and, if present, benzyl alcohol can be used when formulating a topical composition via a solution as mentioned above.

The liquid triturate or other co-solution mixture can be admixed with any compatible pharmacologically acceptable vehicle to form a topical composition. Preferably, the vehicle is an aqueous gel or cream. Carbomer (ie. carboxypolymethylene; carboxyvinyl polymer) is particularly suitable as a gelling agent in said aqueous gel vehicle.

Usually, the concentration of ibuprofen in the topical compositions of the invention will be in the range 0.1 to 20 percent by weight but any pharmacologically active concentration can be used. Preferably, the ibuprofen concentration will be 2 to 12 percent by weight

and especially 3 to 6 percent by weight. Said amounts are by weight based upon the total weight of the topical composition.

The topical compositions of the invention can contain other compatible pharmacologically acceptable additives conventionally used in topical formulations such as antimicrobial agents, colorants, perfumes, Ph modifiers, antioxidants and stabilisers. Further, they can contain other compatible pharmacologically active substances such as other non-steroidal anti-inflammatory agents, steroids, antibiotics and antibacterials.

The present invention is illustrated by the following non-limiting examples.

EXAMPLE 1

4 g Crystalline ibuprofen was triturated with 4 g crystalline menthol to form an oil phase. This oil phase was then mixed with Carbomer, ethanol and water to form a topical gel having the following composition:

Ibuprofen	4 g
Menthol	4 g
Carbomer*	1-2 g
Ethanol	qs
Water	to 100 g

* Carbopol 941

EXAMPLE 2

4 g Crystalline ibuprofen was triturated with 4 g crystalline menthol and 5 g propylene glycol to form an oil phase, which was then mixed with Carbomer, ethanol and water to form a topical gel having the following composition:

Ibuprofen	4 g
Menthol	4 g
Propylene glycol	5 g
Carbomer*	1-2 g
Ethanol	qs
Water	to 100 g

* Carbopol 941

EXAMPLE 3

4 g Crystalline ibuprofen was triturated with 4 g crystalline menthol, 3 g propylene glycol and 3 g benzyl alcohol to form an oil phase, which was then mixed with Carbomer, ethanol and water to form a topical gel having the following composition.

Ibuprofen	4 g
Menthol	4 g
Propylene glycol	3 g
Benzyl alcohol	3 g
Carbomer*	1-2 g
Ethanol	qs
Water	to 100 g

* Carbopol 941

EXAMPLE 4

4 g Crystalline ibuprofen was triturated with 2 g crystalline menthol, 4 g propylene glycol and 4 g benzyl alcohol to form an oil phase, which was then mixed with Carbomer, ethanol and water to form a topical gel having the following composition.

Ibuprofen	4 g
Menthol	2 g
Propylene glycol	4 g
Benzyl alcohol	4 g
Carbomer*	1-2 g
Ethanol	qs
Water	to 100 g

* Carbopol 941

EXAMPLE 5

3.0 g Crystalline ibuprofen was triturated with 1.5 g crystalline menthol to form an oil phase. This oil phase was then mixed with propylene glycol and then added to a second gel of Carbomer, ethanol and water to form a topical gel having the following composition:

Ibuprofen	3.0 g
Menthol	1.5 g
Propylene glycol	6.7 g
Carbomer*	1-2 g
Triethanolamine (85%)	1.25 g
Ethanol	23.0 g
Water	to 100 g

* Carbopol 980

The gel was cloudy in appearance and, under the microscope was seen to contain dispersed microcrystalline material.

EXAMPLE 6

Ibuprofen, menthol and propylene glycol were mixed

together in ethanol and the resultant solution mixed with an aqueous Carbomer gel and subsequently thickened with triethanolamine to provide a topical gel of the same composition as that of Example 5.

The gels of Examples 1 to 6 were found to be completely stable after storage for 6 months at ambient temperatures. At the end of the period of storage there was no significant loss of dissolved ibuprofen through crystallisation.

CLAIMS:

1. A composition comprising a co-solution mixture of ibuprofen and menthol.

2. A topical pharmaceutical composition comprising a co-solution mixture of ibuprofen and menthol in a pharmacologically acceptable vehicle.

3. A topical composition as claimed in Claim 2, wherein the vehicle is an aqueous gel.

4. A topical composition as claimed in Claim 2, wherein the ibuprofen content is 2 to 12 percent by weight of the composition.

5. A topical composition as claimed in Claim 4, wherein said ibuprofen content is 3 to 6 percent by weight of the composition.

6. A composition as claimed in Claim 1, which is a liquid triturate consisting essentially of ibuprofen and menthol.

7. A composition as claimed in Claim 1, comprising benzyl alcohol.

8. A composition as claimed in Claim 7, which is a liquid triturate consisting essentially of ibuprofen, menthol and benzyl alcohol.

9. A composition as claimed in Claim 1, wherein the ibuprofen is present in an amount in the range 50 to 70 percent by weight of the combined weights of ibuprofen, menthol and, if present, benzyl alcohol.

10. A composition as claimed in Claim 1, further comprising a glycol.

11. A composition as claimed in Claim 10, wherein said glycol is propylene glycol.

12. A composition as claimed in Claim 11, which is a liquid triturate consisting essentially of ibuprofen, menthol and propylene glycol.

13. A composition as claimed in Claim 10, wherein the glycol is present in an amount in the range 10 to 70 percent by weight of the combined weights of ibuprofen, menthol, glycol and, if present, benzyl alcohol.

14. A composition as claimed in Claim 13, wherein the amount by weight of glycol is 10 to 30 percent by weight of the triturate.

15. A composition as claimed in Claim 2, comprising ethanol.

16. A method of stabilizing a topical composition comprising ibuprofen which comprises incorporating in said composition an amount of menthol sufficient to form a co-solution mixture with the ibuprofen.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 90/01471

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 31/19, A 61 K 47/10

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0072462 (TOKO YAKUHIN INDUSTRY CO., LTD) 23 February 1983 see page 3, line 15 - page 4, line 26; page 5, line 18 - page 6, line 7, line 24 - page 7, line 17; page 15, Table 2; page 19, Table 3; claims 1-4,9	1-6,16
Y		7-15
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Y	EP, A, 0070525 (TOKO YAKUHIN INDUSTRY CO., LTD) 26 January 1983 see page 3, line 15 - page 4, line 12; page 6, lines 17-25; page 17, Table 7; page 23, Table 12; claims 1,6	7-9
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* Special categories of cited documents: [16]

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"E" earlier document but published on or after the international filing date

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17th January 1991	22.02.91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Alfredo Prein

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	EP, A, 0147146 (AMERICAN HOME PRODUCTS CORPORATION) 3 July 1985 see page 3, lines 17-23; page 4, lines 1-15; page 9, example 2; page 10, example 3; claims 1-8	10-15

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9001471 SA 40753

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0072462	23-02-83	JP-A- 58029706	22-02-83
		US-A- 4545992	08-10-85
EP-A- 0070525	26-01-83	JP-A,B,C 58015909	29-01-83
		CA-A- 1174601	18-09-84
EP-A- 0147146	03-07-85	AU-A- 3683484	27-06-85
		CA-A- 1238275	21-06-88
		JP-A- 60152413	10-08-85
		US-A- 4931283	05-06-90
		US-A- 4933184	12-06-90

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